Support in the Specification

A paragraph has been added to the specification, indicating the priority claimed by the Applicants in the executed Declaration filed by the Applicants on July 13, 2001.

Several specification paragraphs have amended to correct punctuation, to correct spelling, and to delete World Wide Web addresses and substitute the name of the corresponding site in place thereof.

Drawing figure numbers for Figures 1, 2, and 10 have been amended to specifically correspond to correctly identified drawing figure numbers in the replacement drawing sheets.

Claim 28 has been amended to incorporate the recitations of claim 24 (from which it previously depended) and to recite that administration of the isolated protein to a mammal elicits an immune response against *N. meningitidis*, as disclosed in the specification, for example at page 33, line 23, through page 34, line 7. Support for the amendment of claim 32, that the pharmaceutical composition is "immunogenetic," restated from original claim 32 as "a vaccine," is also found at that portion of the specification.

A typographical error in claim 27 has been corrected.

The homology recitation added to claim 30 is disclosed in the specification, for example at page 15, lines 11-13.

Pharmaceutically-acceptable carriers, diluents, and excipients, as recited in amended claim 31, are disclosed in the specification, for example at page 32, lines 11 and 12.

The particular isolated proteins recited in new claims 33 and 34 are disclosed in Example 4 of the specification, for example at page 44, line 12, through page 45, line 4.

All of the claims other than 28 have been amended such that they depend, directly or indirectly, from claim 28, the only independent claim.

Replacement drawing sheets 1-13, 24, and 25 have been submitted. These replacement drawing sheets have been altered simply to conform the drawing figure numbers to Patent Office convention.

For the foregoing reasons, the Applicants respectfully contend that the additions and amendments made herein do not include new matter.

Priority Claim

The Examiner did not check box 14 of the Office Action Summary sheet. The Examiner is requested to acknowledge the Applicants' claim of priority to U.S. Provisional Application serial number 60/177,917, filed January 25, 2000.

Election of Species

The Applicants gratefully acknowledge the Examiner's withdrawal of the requirement to elect specific residues of elected SEQ ID NO: 11. However, the Examiner considers claims 26, 27, and 29 to be withdrawn from consideration. In the Examiner's view, these claims are directed to non-elected species. The Applicants remind the Examiner that SEQ ID NO: 11 is a consensus sequence that, by its definition (e.g., see the sequence listing) incorporates each of SEQ ID NOs: 1-10. The Applicants respectfully suggest that claims 26, 27, and 29 should not be considered withdrawn, and request that the Examiner consider the merits of these three claims together with the other pending claims.

Objections to the Specification

In items 2 and 3 of the Office Action, the Examiner objects to the specification. In item 2, the Examiner objects to inclusion of World Wide Web addresses. The Applicants have removed each of these addresses and substituted in place thereof the name of the corresponding web site. In item 3, the Examiner objects to reference to "FIG. 14." This reference has been changed to "FIGS. 14A-14G" in conformity with the drawing figure numbers used on the drawings. The Applicants respectfully contend that these amendments alleviate the Examiner's objections, and request that the Examiner withdraw the objections.

Formal Drawings

In response to the objections noted by the Draftsman on the PTO form 948, the Applicants have submitted replacement drawing sheets 1-13, 24, and 25. The Applicants respectfully contend that the changes made to the drawing sheets (i.e., merely changing the drawing figure numbers to conform to Patent Office convention) overcome the Draftsperson's objections and request that the objections to the drawings be withdrawn.

Claim Rejections Pursuant to 35 U.S.C. § 112, First Paragraph (Written Description)

Claims "24-23" (assumed to mean 24 and 25), 28, and 30-32 were rejected pursuant to 35 U.S.C. § 112, first paragraph, in item 5 of the Office Action. Claim 24 has been canceled, and its recitations have been incorporated into claim 28. In the Examiner's view, the specification does not provide an adequate written description of the full scope of isolated proteins recited in the claims. In particular, the Examiner objects that the genus of claimed proteins is "highly variant" and that the species disclosed in the specification are not sufficiently representative of the claimed genus.

The Examiner's suggestion that the claimed genus is "highly variant" appears to be based on the Examiner's belief (see the Office Action at the first sentence of the paragraph beginning on page 5) that a skilled artisan cannot envision the detailed structure of allelic variants or of fragments of SEQ ID NO: 11. The Applicants respectfully suggest that the Examiner does not appreciate what the Applicants have invented.

The invention that must be examined by the Examiner is the subject matter that is claimed. In this application, the claims recite an isolated protein comprising amino acids from a conserved region of the consensus sequence, SEQ ID NO: 11. Because this claim is written in 'open' ("comprising") format, the identity of other residues that may be present in the isolated protein is substantially immaterial. For this reason, the Applicants do not accept the Examiners reasoning that "the genus is highly variant." The claimed genus is not highly variant, but instead highly conserved. The Applicants have discovered minimum sequences that are necessary in an isolated protein that elicits an immune response against multiple (or all) strains of *N. meningitidis* (i.e., isolated proteins that are cross-reactive against these strains). These minimum sequences include at least twelve contiguous residues from one of the conserved regions (i.e., C1-C5) of SEQ ID NOs: 1-11 that are identified in the specification (e.g., see Figures 1 and 2). Cross-reactive proteins can have additional sequences, but only the Applicants have discovered how little sequence need be included. For these reasons, a skilled artisan is able to envision the relevant structure of the isolated proteins that are claimed. It is this relevant structure that is recited in the claims.

The Applicants believe that the Examiner has unduly focused on potential sequence variability among NhhA polypeptides, allelic variants, and the like, despite the fact that the claimed invention is directed to use of the conserved regions of NhhA polypeptides. Instead of focusing on potential sequence variability in unimportant regions of the claimed proteins, the Examiner must analyze compliance of what is claimed with the written description requirement. The variability of any other portion of the claimed proteins is substantially immaterial, and would be recognized by a skilled artisan as such. Even then, the embodiments wherein this other (i.e., non-relevant) portion of the protein interferes with the conserved immunogenic (i.e., relevant) portion of the protein recited in the claims are excluded from the claimed genus by reciting in claim 28 that the claimed protein elicits an immune response when it is administered to a mammal.

The Applicants respectfully contend that the specification provides an adequate written description of the information that is necessary for a skilled artisan to envision and design the structure of any of the isolated proteins recited in the claims, and that the written description requirement is therefore satisfied. Reconsideration and withdrawal of the Examiner's rejection of claims 25, 28, and 30-32 pursuant to 35 U.S.C. § 112, first paragraph (written description requirement), are respectfully requested for this reason alone.

There is an alternative reason why the Examiner should withdraw the written description rejection. It is settled law that compliance with the written description requirement must be considered in light of the state of the art and the knowledge of the skilled artisan at the time the application was filed. "The primary concern is factual and depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure" (*VasCath, Inc. v. Mahurkar*, 19 USPQ2d 1111 (Fed. Cir. 1991), quoting *In re Wertheim*, 191 USPQ 90, 96 (C.C.P.A. 1976)). As explained in that decision, the purpose of the written description requirement is broader than to merely explain how to make and use the invention. The applicant must also convey with reasonable clarity to one skilled in the art that, as of the filing date, he or she was in possession of the invention.

"[I]t is not necessary that the application describe the claimed invention in *ipsis verbis;* all that is required is that it reasonably convey to persons skilled in the art that, as of the filing date thereof, the inventor had possession of the subject matter later claimed by him." *In re*

Edwards, 196 USPQ 465,467 (C.C.P.A. 1978) (citing *In re Lukach, 169 USPQ 795* (C.C.P.A. *1971); In re Driscoll, 195 USPQ 434 (C.C.P.A. 1977)).* This point was reiterated by the Court of Appeals for the Federal Circuit, in *In re Kaslow,* 217 USPQ *1089, 1096* (Fed. Cir. *1983),* citing *In re Edwards,* "The test for determining compliance with the written description requirement is whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter, rather than the presence or absence of literal support in the specification for the claim language." Thus, the Applicants are not required to explicitly disclose all possible embodiments of what is claimed.

In *Regents of the Univ. of California v. Eli Lilly & Co.,* 43 USPQ2d 1398 (Fed. Cir. 1997), it was held that patent applicants are not required to disclose every species within a claimed genus; the written description requirement can be satisfied with a description of a representative number of species of a claimed genus, particularly if structure common to the genus is also provided. In this application, the Applicants have disclosed the conserved sequences (i.e., structure), as least twelve residues of which must be present, have disclosed portions of the claimed proteins for which the sequence is not important, and have disclosed numerous examples of the claimed proteins. The Applicants respectfully contend that the specification demonstrates that, in view of what was known in the art and by the skilled artisan at the time the application was filed, the Applicants were in possession of the entire invention that is now claimed. For this alternative reason (alone or in combination with the preceding reason), the Examiner should reconsider and withdraw the written description rejection of claims 25, 28, and 30-32 pursuant to 35 U.S.C. § 112, first paragraph.

Claim Rejections Pursuant to 35 U.S.C. § 112, First Paragraph (Enablement)

In item 7 of the Office Action (no item 6 appears in the Office Action, and all pages of the Office Action appear to be present), the Examiner rejects claims 31 and 32 pursuant to 35 U.S.C. § 112, first paragraph. In the Examiner's view, the enablement provided by the specification is not commensurate in scope with these claims. The Examiner's concern appears to center around use of the term "vaccine."

Claim 32, originally reciting a vaccine, has been amended to recite that the composition is immunogenic. Claim 32 is dependent on claim 31 directed to a pharmaceutical composition.

As conceded by the Examiner, the description provides ample working evidence to show that the isolated proteins described in the specification can be delivered as an immunogenic composition to laboratory animals, which immunogenic composition induces antibody responses to the isolated protein (e.g., see Example 10).

In framing his rejection of former claims 31 and 32, the Examiner has focused on an assertion that "the art is replete with instances where even well characterized antigens that induce an *in vitro* neutralizing antibody response fail to elicit *in vivo* protective immunity." The Applicants submit that claims 31 and 32, as amended, do not recite that the composition is a vaccine or that it must provide a protective immune response when administered to an individual. The Applicants contend that the description shows efficacy of the compositions of the invention in inducing an immune response and, as such, may be readily made and used for the purposes of producing antibodies that recognize NhhA polypeptides.

For these reasons, the Applicants respectfully submit that claims to immunogenic compositions are fully enabled and should not be rejected on the grounds raised by the Examiner. Reconsideration and withdrawal of the Examiner's enablement rejection of claims 31 and 32 pursuant to 35 U.S.C. § 112, first paragraph, are respectfully requested.

Claim Rejections Pursuant to 35 U.S.C. § 112, Second Paragraph

Claims 24 and 31 stand rejected pursuant to 35 U.S.C. § 112, second paragraph.

The Examiner objects to the term "capable of" in claim 24. Use of this term has been discontinued, and the Examiner's rejection is believed to be moot.

The Examiner rejects claim 31 on the basis that no pharmaceutical carrier is recited. Claim 31, as amended, recites that the compositions includes at least one pharmaceutical carrier, excipient, or diluent, and the Examiner's rejection is believed to be moot.

For the foregoing reasons, the Applicants respectfully request that the Examiner reconsider and withdraw the rejections of claims 24 and 31 pursuant to 35 U.S.C. § 112, second paragraph.

Claim Rejections Pursuant to 35 U.S.C. § 102(e) over Peak

Claims 24, 25, 31, and 32 stand rejected pursuant to 35 U.S.C. § 102(e) over Peak (U.S. Patent no. 6,197,312). Claim 28 was not rejected.

The Applicants have incorporated the recitations of canceled independent claim 24 into claim 28, and the Examiner's rejection should therefore not apply to claims 25, 28, 31, and 32 for that reason. Reconsideration and withdrawal of the Examiner's rejection of claims 25, 31, and 32 pursuant to 35 U.S.C. § 102(e) over Peak are respectfully requested.

Claim Rejection Pursuant to 35 U.S.C. § 102(b) over Zhao

Claim 30 stands rejected pursuant to 35 U.S.C. § 102(b) over Zhao (1990, Mol. Gen. Genet. 223(1):163-166). The Examiner indicates that Zhao discloses a protein that has 19.2% sequence similarity to SEQ ID NO: 11. Claim 30 has been amended to recite that the claimed allelic variant exhibits at least 80% sequence identity to an isolated protein recited in claim 24. The protein disclosed in Zhao does not satisfy this criterion, and the Examiner's rejection is believed to be overcome for this reason. Reconsideration and withdrawal of the Examiner's rejection of claim 30 pursuant to 35 U.S.C. § 102(b) over Zhao are respectfully requested.

Summary

In view of the arguments and amendments presented herein, the Applicants believe that each of claims 25-34 is in condition for allowance. Reconsideration and allowance of these claims are respectfully requested at the earliest possible time.

Respectfully submitted,

IAN RICHARD ANSELM PEAK *ET AL.*

October 15, 2002 By: _____
(Date)

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Enclosures: Marked-Up Copy of Amended Specification Paragraphs
Marked-Up Copy of Claims Amended
Clean Copy of Claims, as Amended
Replacement Drawing Sheets 1-13, 24, and 25

Marked-Up Copy of Amended Specification Paragraphs in the Response to the Office Action Dated July 12, 2002

Please delete the paragraph that appears at page 3, lines 27-31, and substitute the following paragraph in place thereof.

In particular embodiments, the isolated protein has an amino acid sequence as set forth in any one of FIGS. 5 to 9 (SEQ ID NOS: 23 to 27) which are examples of "*modified NhhA polypeptides of the invention*". In ~~FIG. 14~~ FIGS. 14A-14G (SEQ ID NOS: 33 to 39) further examples are provided of "mature" polypeptides predicted to result of removal of N-terminal signal sequences.

Please delete the paragraph that appears at page 6, line 25, through page 7, line 7, and substitute the following paragraph in place thereof.

Table 1: Identification of amino acids of the conserved regions (C1, C2, C3, C4 and C5) and variable regions (V1, V2, V3 and V4) of an NhhA polypeptide from each of ten (10) indicated strains of *N. meningitidis*. Relevant SEQ ID NOS are also indicated. Column 1 = strain designation. SEQ ID NOS: 1-9 were previously described in copending application WO99/31132; the sequences of NhhA and *nhhA* of strain Z2491 were obtained from ~~*http://www.sanger.ac.uk/Projects/N_meningitidis/*~~ the database of the Wellcome Trust/Sanger Institute genomic sequencing project for *N. meningitidis*; column 2 = amino acid numbering of C1 region; column 3 = amino acid numbering of V1 region; column 4 = amino acid numbering of C2 region; column 5 = amino acid numbering of V2 region; column 6 = amino acid numbering of C3 region, column 7 = amino acid numbering of V2 region; column 8 = amino acid numbering of C4 region; column 9 = amino acid numbering of V4 region; column 10 =

amino acid numbering of C5 region. Note that the amino acid numbering of the consensus sequence (SEQ ID NO:_11) is also indicated.

Please delete the paragraph that appears at page 7, lines 9-17, and substitute the following paragraph in place thereof.

FIG. 1 (comprising FIGS. 1A-1E): Amino acid sequence alignments of NhhA polypeptide amino acid sequences from ten (10) *N. meningitidis* strains (SEQ ID NOS: 1-10) together with consensus sequence (SEQ ID NO:_11). Strain names and polypeptide sequences used in this alignment correspond to the strain names and SEQ ID NOS in column 1 of Table 1. Amino acids are indicated by standard single letter abbreviations. Consensus amino acids are shown only where residues are completely conserved. Conserved regions (double underlined, labeled C1, C2, C3, C4, C5) and variable regions (single underlined, labeled V1, V2, V3, V4) are indicated under the consensus sequence.

Please delete the paragraph that appears at page 7, lines 18-21, and substitute the following paragraph in place thereof.

FIG. 2 (comprising FIGS. 2A-2H): Nucleotide sequence alignment of *nhhA* nucleic acids from ten (10) *N. meningitidis* strains, which sequences encode the amino acid sequences of FIG. 1. Regions C1, C2, C3, C4, C5 and V1, V2, V3, V4 are as described in FIG. 1 and Table 1.

Please delete the paragraph that appears at page 8, line 28, through page 9, line 4, and substitute the following paragraph in place thereof.

FIG. 10 (comprising Figures 10A and 10B): Amino acid sequence alignments of wild type and NhhA deletion mutant polypeptide sequences. These polypeptides were produced as described in Example 2, Example 3, Example 4 and Example 5. Amino acids are indicated by the one letter abbreviation. Conserved regions ~~labelled~~ labeled C1, C2, C3, C4 and C5 corresponding to those defined in Table 1 and FIG. 1 are indicated by double underlining of full length sequences from H41 and PMC21, and variable regions ~~labelled~~ labeled V1, V2, V3, V4 corresponding to those defined in Table 1 and FIG. 1 are indicated by single underlining of full length sequences from H41 and PMC21.

Please delete the paragraph that appears at page 42, line 19, through page 52, line 4, and substitute the following paragraph in place thereof.

The resulting plasmid, pIP52(PMC21), was linearized by restriction digestion and used to transform *N. meningitidis* strain 7G2 using the method described by Janik *et al*, 1976, Journal of Clinical Microbiology ~~4~~ :71. Transformants were selected by overnight incubation at 37 °C in 5% CO_2 on solid media containing 100 µg/ml kanamycin. Kanamycin resistant colonies were selected, subcultured overnight and screened for over-expression of NhhA polypeptide by separating total cell proteins electrophoretically on 10% SDS-PAGE followed by transfer to nitrocellulose membrane using a Semi-Dry Blotter (BioRad). The membrane was then incubated sequentially with rabbit anti-NhhA sera (as described in International Publication WO99/31132) and alkaline-phosphatase conjugated anti-Rabbit IgG (Sigma) before colorimetric detection with NBT/BCIP (Sigma). One clone was isolated which expressed NhhA polypeptide at a higher level compared with the parental strain (FIG. 11). Analysis of the predicted amino acid sequence using the computer program SIGCLEAVE (part of the eGCG suite of programs hosted at ~~www.angis.org.au~~ the World Wide Web site of the

Australian National Genomic Information Service {ANGIS}) indicates that the first 51 amino acids will be cleaved to produce the mature polypeptide (FIG. 14; SEQ ID NO:_33).

Please delete the paragraph that appears at page 43, lines 9-19, and substitute the following paragraph in place thereof.

The NhhA protein encoded by the *nhhA* gene of *N. meningitidis* strain H41 was over expressed using the same methods as described in Example 2. This created a recombinant nucleic acid expression construct (open reading frame shown in SEQ ID NO:_13) which encodes a polypeptide of 591 amino acids as shown in SEQ ID NO: 2. In this example the resulting plasmid pIP52(H41) was linearized, and transformed into *N. meningitidis* strain 7G2. Kanamycin resistant colonies were analysed and one was chosen which when examined by Western immunoblot, demonstrated overexpression of NhhA. (FIG. 11). Analysis of the predicted amino acid sequence using the computer program SIGCLEAVE (part of the eGCG suite of programs hosted at ~~www.angis.org.au~~ the World Wide Web site of the Australian National Genomic Information Service {ANGIS}) indicates that the first 51 amino acids will be cleaved to produce the mature polypeptide (FIG. 14; SEQ ID NO:_34).

Please delete the paragraph that appears at page 44, line 29, through page 45, line 4, and substitute the following paragraph in place thereof.

Analysis of the predicted amino acid sequence using the computer program SIGCLEAVE (part of the eGCG suite of programs hosted at ~~www.angis.org.au~~ the World Wide Web site of the Australian National Genomic Information Service {ANGIS}) indicates that the first 51 amino acids will be cleaved to produce the mature polypeptide (FIG. 14; SEQ ID NO: 35). To confirm the presence of a cleavable signal sequence and to confirm the identity of the

over expressed protein, outer membrane proteins were semi-purified by isolating the fraction that is insoluble in the detergent sarkosyl.

Please delete the paragraph that appears at page 46, lines 17-20, and substitute the following paragraph in place thereof.

Analysis of the predicted amino acid sequence using the computer program SIGCLEAVE (part of the eGCG suite of programs hosted at ~~www.angis.org.au~~ the World Wide Web site of the Australian National Genomic Information Service {ANGIS}) indicates that the first 51 amino acids will be cleaved to produce the mature polypeptide (FIG. 14; SEQ ID NO: 36).

Please delete the paragraph that appears at page 48, lines 13-16, and substitute the following paragraph in place thereof.

Analysis of the predicted amino acid sequence using the computer program SIGCLEAVE (part of the eGCG suite of programs hosted at ~~www.angis.org.au~~ the World Wide Web site of the Australian National Genomic Information Service {ANGIS}) indicates that the first 51 amino acids will be cleaved to produce the mature polypeptide (FIG. 14; SEQ ID NO: 37).

Please delete the paragraph that appears at page 49, lines 14-27, and substitute the following paragraph in place thereof.

The amplification products HOMP5'/SO-E and SO-F/HO3'AN will be purified from agarose gel following separation by electrophoresis, and will be mixed, and subjected to further amplification using primers HOMP5' and HO3'AN. The resulting product encodes amino acids 1-52 and 211-591 of wild-type NhhA of PMC21. This amplification product will be subjected to restriction digestion with *Eag*I and *Nco*I, and cloned into pCO14K. This recombinant molecule contains regions C1, C4, V4 and C5 thus deleting regions V1-3 and C2-3. The nucleotide sequence of the open reading frame is shown in FIG. 8 and SEQ ID NO: 31, and the predicted polypeptide sequence derived from this nucleotide sequence is shown in FIG. 8 and SEQ ID NO: 26. Analysis of the predicted amino acid sequence using the computer program SIGCLEAVE (part of the eGCG suite of programs hosted at ~~www.angis.org.au~~ the World Wide Web site of the Australian National Genomic Information Service {ANGIS}) indicates that the first 51 amino acids will be cleaved to produce the mature polypeptide (FIG. 14; SEQ ID NO: 38).

Please delete the paragraph that appears at page 51, line 19, through page 52, line 2, and substitute the following paragraph in place thereof.

The amplification products HOMP5'/SO-I and SO-J/HO3'AN will be purified from agarose gel following separation by electrophoresis, and will be mixed, and subjected to further amplification using primers HOMP5' and HO3'AN. The resulting product encodes amino acids 1-52, 103-114, 125-188, 211-229, and 237-591 of wild-type NhhA of strain PMC21. The resulting product will be subjected to restriction digestion with *Eag*I and *Nco*I, and cloned into pCO14K. This recombinant molecule contains regions C1, C2, C3, C4 and C5, thus deleting regions V1, V2, V3, and V4. The nucleotide sequence of the open reading frame is shown in FIG. 9 and SEQ ID NO: 32, and the predicted polypeptide sequence derived from

this nucleotide sequence is shown in FIG. 9 and SEQ ID NO: 27. Analysis of the predicted amino acid sequence using the computer program SIGCLEAVE (part of the eGCG suite of programs hosted at ~~www.angis.org.au~~ the World Wide Web site of the Australian National Genomic Information Service {ANGIS}) indicates that the first 49 amino acids will be cleaved to produce the mature polypeptide (FIG. 14; SEQ ID NO: 39).

Marked-Up Copy of Claims Amended in the Response to the Office Action Dated July 12, 2002

25. (Amended) The isolated protein of claim ~~24~~ 28, wherein the conserved region is selected from the group consisting of:

(i) residues 1 to 50 of SEQ ID NO:11;

(ii) residues 109 to120 of SEQ ID NO:11;

(iii) residues 135 to198 of SEQ ID NO:11;

(iv) residues 221 to 239 of SEQ ID NO:11; and

(v) residues 249 to 604 of SEQ ID NO:11.

26. (Amended) The isolated protein of claim ~~24~~ 28, wherein the protein comprises at least twelve contiguous amino acids of a sequence selected from the group consisting of SEQ ID NOs: 1-10.

27. (Amended) The isolated protein of claim ~~24~~ 28, wherein the isolated protein has an amino acid sequence selected from the group consisting of:

(i) residues 1 to 50 of SEQ ID NO: 1;

(ii) residues 1 to 50 of SEQ ID NO: 2;

(iii) residues 1 to 50 of SEQ ID NO: 3;

(iv) residues 1 to 50 of SEQ ID NO: 4;

(v) residues 1 to 50 of SEQ ID NO: 5;

(vi) residues 1 to 50 of SEQ ID NO: 6;

(vii) residues 1 to 50 of SEQ ID NO: 7;

(viii) residues 1 to 50 of SEQ ID NO: 8;

(ix) residues 1 to 50 of SEQ ID NO: 9;

(x) residues 1 to 50 of SEQ ID NO: 10;

(xi) residues 125 to 188 of SEQ ID NO: 1;

(xii) residues 125 to 188 of SEQ ID NO: 2;

(xiii) residues 122 to 185 of SEQ ID NO: 3;

(xiv) residues 127 to 190 of SEQ ID NO: 4;

(xv) residues 125 to 188 of SEQ ID NO: 5;

(xvi) residues 132 to 195 of SEQ ID NO: 6;

(xvii) residues 131 to 194 of SEQ ID NO: 7;

(xviii) residues 131 to 194 of SEQ ID NO: 8;

(xix) residues 127 to 190 of SEQ ID NO: 9;

(xx) residues 125 to 188 of SEQ ID NO: 10;

(xxi) residues 211 to 229 of SEQ ID NO: 1;

(xxii) residues 206 to 224 of SEQ ID NO: 3;

(xxiii) residues 237 to 591 of SEQ ID NO: 1;

(xxiv) residues 237 to 592 of SEQ ID NO: 2;

(xxv) residues 235 to 589 of SEQ ID NO: 3;

(xxvi) residues 239 to 594 of SEQ ID NO: 4;

(xxvii) residues 237 to 591 of SEQ ID NO: 5;

(xxviii) residues 244 to 599 of SEQ ID NO: 6;

(xxix) residues 243 to 598 of SEQ ID NO: 7;

(xxx) residues 243 to 598 of SEQ ID NO: 8~~.~~;

(xxxi) residues 239 to 594 of SEQ ID NO:9; and

(xxxii) residues 237 to 592 of SEQ ID NO:10.

28. (Amended) ~~The~~ An isolated protein ~~of claim 24 further~~ comprising at least twelve contiguous amino acids of a conserved region of SEQ ID NO: 11 and one or more variable (V) region amino acids of ~~an NhhA polypeptide~~ SEQ ID NO: 11, wherein the isolated protein is not a wild-type NhhA polypeptide and wherein upon administration to a mammal the protein elicits an immune response against one or more strains of *N. meningitidis*.

29. (Amended) The isolated protein of claim ~~24~~ 28, having an amino acid sequence selected from the group consisting of: SEQ ID NO: 23; SEQ ID NO: 24, SEQ ID NO: 25; SEQ ID NO: 26; SEQ ID NO: 27; SEQ ID NO: 33; SEQ ID NO: 34 SEQ ID NO: 35; SEQ ID NO: 36; SEQ ID NO: 37; SEQ ID NO: 38; and SEQ ID NO: 39.

30. (Amended) An allelic variant of the isolated protein of claim ~~24~~ 28, having at least 80% amino acid sequence identity to the isolated protein.

31. (Amended) A pharmaceutical composition comprising one or more isolated proteins according to claim ~~24~~ 28 and a pharmaceutically-acceptable carrier, diluent, or excipient.

32. (Amended) The pharmaceutical composition of claim 31 which is ~~a vaccine~~ immunogenic.